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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| IN RE APPLICATION OF: | : | |
| Anne-Françoise BURNOL et al. | : | GROUP ART UNIT: 1647 |
| SERIAL NO.: 09/936,697 | : | EXAMINER: NICHOLS, C.J. |
| FILED: March 14, 2000 | : | |
| FOR: Grb14 AND THE INSULIN RECEPTOR AND SCREENING OF NOVEL MEDICINES | | |

**DECLARATION UNDER 37 C.F.R. 1.132**

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C.

SIR:

I, Anne-Françoise BURNOL, do hereby declare and say as follows:

1. That I am a graduate of Endocrinology and received my PHD degree in the year 1983.

2. That I have been employed by CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE for 20 years as a researcher in the field of Life Sciences.

3. That my understanding of Kasus-Jacobi et al. article, US Patent 5,840,536 and O'Neill et al. article, is the following:

**Kasus-Jacobi et al. article**

This document, whom I am one of the Authors, concerns the identification of the rat adapter Grb14 as an inhibitor of insulin actions. The main aim of this article was to

identify new proteins implicated in signal transduction. This article describes therefore a protein displaying a highly homology with the human Grb14, a member of the Grb7 subfamily of adapters.

This new protein, named rGrb14 is potentially a new effector of the insulin receptor.

In rGrb14, a region different from the SH2 domain has been identified as the main binding domain with the insulin receptor.

This region, named PIR, is homologous to the PBS domain previously described in Grb10.

I consider that said document:

- teaches that the fragments PIR, SH2 and PIR-SH2 of **rGrb14** interact with the receptor of insulin (see page 26030 and figure 6); however, it is specified that rGrb14 binds to activated insulin receptors but is not a substrate of the tyrosine kinase (page 26032, right column).

- defines a region of interaction protein-protein, the PIR domain, which is present in rGrb14 and binds (page 26033, left column) specifically to the receptor of phosphorylated insulin.

- indicates that the mechanism of binding of these proteins mediated by these two domains (PIR, SH2) is still not known ; the question about the type of binding remains since as stated in page 26034, right column, last paragraph:

*" [...]rGrb14 could act in two opposite directions by interacting with this loop; it could either inhibit the tyrosine kinase activity by masking access to the catalytic site, or it could maintain the enzyme in an active conformation by stabilizing the phosphorylated loop"*

- only shows that the PIR domain of rGrb14 interacts strongly with the receptor of insulin (figure 6 and page 26030, 2nd column, 3rd paragraph) and states that the PIR et SH2 domains of rGrb14 and of Grb10 are then able to bind separately to the receptor of insulin, the presence of the two domains being however necessary in Grb10, for inhibiting the activity of the receptor of IGF (page 26033, right column, 2nd paragraph).

Therefore, Kasus-Jacobi *et al.* would not incite the skilled person in the art to use exclusively the PIR domain of a protein from the Grb7 family, and more specifically hGrb14, with the receptor of activated insulin in a method for screening molecules active in diabetes and obesity, since this document does not suggest that the PIR domain presents a direct inhibitory activity on the activity of tyrosine kinase from the receptors of insulin.

Since it is clearly stated in Kasus-Jacobi *et al.* that the proteins from the Grb7 family do not present the same properties (behaviour depending on the different receptors), the skilled person in the art has no reason to extrapolate on the results obtained from rGrb14 and Grb10 to all the other proteins of the Grb7 family.

Thus it clearly emerges from the foregoing that Kasus-Jacobi *et al.* neither teach, nor suggest the unexpected results of the present invention, i.e. that the PIR domain alone has an activity as inhibitor of the tyrosine kinase of the insulin receptor, which is equivalent to that of the whole protein.

**US Patent 5,840,536**

This document relates essentially to human GrbIR-I growth-factor receptor binding protein Insulin receptor is a cytoplasmic signalling molecule containing a SH2 domain-interaction of Grb-IR.

US 5,840,536 also teaches a method of assaying for a molecule that modulates GrbIR-1 function; however, said method does not imply any interaction with the insulin receptor (see column 3 of said Patent).

This document states (columns 10 and 11) that inhibition of GrbIR-I could be effected through antagonism of the SH2 domain/phosphorylated IR interaction or through inhibition of the binding of the PH domain to phosphatidylinositol 4,5 biphosphate.

**O'Neill et al. article**

This document describes the interaction of a Grb-IR splice variant with the insulin and insulin-like growth factor I receptors.

More precisely, said document teaches that Grb-IR1 is a human homolog of Grb10, a member of the Grb7 protein family.

4. That none of the hereabove mentioned documents neither teaches nor suggests that the PIR domain or a fragment thereof of the hGrb14 protein could be used to modulate the tyrosine kinase activity of the insulin receptor.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any Patent issued thereon.

2003, november 10th
Date

signature

Anne-Françoise BURNOL
(Print or type name)